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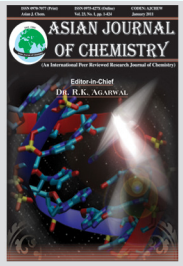

Synthesis of Trisubstituted 1,2,4-Triazines in Presence of $NaHSO_4/SiO_2$

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An efficient method for the synthesis of trisubstituted 1,2,4-triazines, phenanthro-1,2,4-triazines and acenaphtho-1,2,4-triazines derivatives by three-component condensation of benzil or phenanthrene-9,10-dione or acenaphthylene-1,2-dione, with acid hydrazides and ammonium acetate using sodium bisulfate adsorbed on silica gel ($NaHSO_4/SiO_2$) as catalyst is reported.

Key Words: $NaHSO_4/SiO_2$, 1,2,4-Triazines, Solvent-free conditions.

INTRODUCTION

The 1,2,4-triazine ring is a prominent structural core system found in numerous biologically active compounds. In recent years, 1,2,4-triazine compounds have been reported to possess biological activities as anti-AIDS[1], anticancer[2], antimicrobial[3-6], antiviral[7,8] and antifungal[9] activities.

Recently some 1,2,4-triazine derivatives have been identified as potent p38α MAP kinase inhibitors[6]. In addition, 1,2,4-triazines are versatile synthetic building blocks from which a wide-range of heterocyclic systems can be accessed *via* an inverse-electron-demand Diels-Alder sequence[7,8].

The three-component condensation of 1,2-diketones with acyl hydrazides and ammonium acetate is a straightforward synthesis of these compounds. Recently, this condensation has been catalyzed by SiO_2/Et_3N[9,10] and $[Hbim]BF_4$[11]. This reaction is a prolong reaction and affords low yields (< 30 %). Although these methods have a lot of potential, they suffer also from the use of solvents, toxic agents that can be associated with the mixture of products and lack of generality. In addition, they are unsuitable for or cannot be applied for the synthesis of structurally diverse 1,2,4-triazines. On the other hand, it appears that there has been a little interest in the synthesis of phenanthro-1,2,4-triazines and acenaphtho-1,2,4-triazines. Therefore, to avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time, recyclability and simple work-up for the preparation of 1,2,4-triazines under neutral, mild and practical conditions is of prime interest.

Sodium bisulfate adsorbed on silica gel ($NaHSO_4/SiO_2$)[12] has immerged as a very useful catalyst in various organic transformations, including acetylation of alcohols and amines[13], synthesis of homoallylic amines[14], selective deprotection of *t*-butyldimethylsilyl (TBDMS) ethers[15], synthesis of tetra substituted imidazoles[16].

In view of its inherent properties like environmental compatibility, greater selectivity, operational simplicity, moisture-insensitive, non-corrosive nature and ease of isolation, it is therefore, interest to us to find out the behaviour of the reagent system, $NaHSO_4$ supported on silica gel (230-400 mesh) in the synthesis of trisubstituted 1,2,4-triazines, phenanthro-1,2,4-triazines and acenaphtho-1,2,4-triazines derivatives.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were obtained on a Unicom Galaxy Series FTIR 5000 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were determined on a Bruker Avance 300 MHz spectrometer. Elemental analyses were performed by using a CHN analyses on a Vario EL III elemental analyzer.

Preparation of the supported catalyst: To a suspension of 1.5 g of silica gel (Merck, Silica gel 0.063-200 mm) in 20 mL of water *ca.* 0.7 g $NaHSO_4 \cdot H_2O$ was added. The suspension stirred at room temperature for 0.5 h, then water was evaporated under reduced pressure and the residue dried at 120 °C for 3 h.

General procedure for preparation of 6a-f, 7a-c and 8a-d: A mixture of 0.5 mmol benzil or phenanthrene-9,10-dione or acenaphthylene-1,2-dione, acid hydrazide (0.5 mmol), ammonium acetate (1.5 mmol) and $NaHSO_4/SiO_2$ (0.1 g) was thoroughly mixed in a mortar and it was heated on the oil bath at 125 ºC for 4.0-4.5 h. The contents were cooled to room

temperature and mixed thoroughly with 3 × 10 mL of acetone. The solid inorganic material was filtered off. After separation of solid, the solvent was evaporated under reduced pressure. The resulting solid residue was purified by recrystallization from acetone-water (15:1 v:v).

5,6-Diphenyl-3-(pyridin-4-yl)-1,2,4-triazine (6a): IR (KBr, ν_{max}, cm^{-1}): 3047, 2924, 1595, 1500, 1446. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 7.41-7.66 (10H, m, H_{arom}), 8.43 and 8.87 (4H, 2d, ^3J = 4.5 Hz, $H_{py.}$). Anal. calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 76.77; H, 4.31; N, 17.68.

3-(Furan-2-yl)-5,6-diphenyl-1,2,4-triazine (6b): IR (KBr, ν_{max}, cm^{-1}): 1585, 1491. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 6.83 (1H, d, $3J$ = 1.74 Hz, H_{furan}), 7.41-7.60 (11H, m, H_{arom}), 8.10 (1H, d, ^3J = 0.9 Hz, H_{furan}). ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 113.37, 115.58, 129.21, 129.48, 129.79, 129.89, 130.11, 131.09, 135.82, 135.91, 147.55, 149.73, 155.29, 155.64, 156.24 (arom).

5,6-Diphenyl-3-(pyridin-3-yl)-1,2,4-triazine (6c): IR (KBr, ν_{max}, cm^{-1}): 3100, 1575, 1510. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 7.42-7.80 (11H, m, H_{arom}), 8.87 (1H, d, ^3J = 4.2 Hz, H_{py}), 9.22 (1H, d, ^3J = 8 Hz, H_{py}), 9.90 (1H, s, H_{py}). Anal. calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 76.89; H, 4.28; N, 17.75.

3-(5,6-Diphenyl-1,2,4-triazin-3-yl)naphthalen-2-ol (6d): IR (KBr, ν_{max}, cm^{-1}): 3205, 3115, 1653, 1599. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 7.35-7.68 (13H, m, H_{arom}), 7.80 (1H, d, ^3J = 8.1 Hz, $H_{naphth.}$), 8.05 (1H, d, ^3J = 8.1 Hz, $H_{naphth.}$), 9.12 (1H, s, $H_{naphth.}$), 12.28 (1H, s, OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 112.07, 119.79, 124.27, 126.39, 127.71, 129.01, 129.58, 129.89, 130.34, 131.09, 131.53, 135.43, 135.62, 136.92, 155.95, 156.28, 157.39, 162.21 (arom).

3,5,6-Triphenyl-1,2,4-triazine (6e): IR (KBr, ν_{max}, cm^{-1}): 1520, 1489, 1392. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 7.28-7.90 (13H, m, H_{arom}), 8.70 (2H, m, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C: 128.48, 128.56, 128.64, 128.89, 129.43, 129.68, 129.92, 130.87, 131.77, 134.38, 135.35, 135.77, 155.48, 155.95, 161.10 (arom).

4-(5,6-Diphenyl-1,2,4-triazin-3-yl)phenol (6f): IR (KBr, ν_{max}, cm^{-1}): 3443, 3053, 1608, 1506, 1444. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 6.98 (2H, d, ^3J = 8.61 Hz, H_{phenol}), 7.38-7.61 (10H, m, H_{arom}), 8.40 (2H, d, ^3J = 8.61 Hz, H_{phenol}), 10.18 (1H, s, OH). Anal. calcd. for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.91;. Found: C, 76.77; H, 4.25; N, 13.12.

2-(Phenanthro[9,10-e][1,2,4]triazin-3-yl)naphthalen-1-ol (7a): IR (KBr, ν_{max}, cm^{-1}): 3441 (OH), 3057, 1664, 1628, 1597, 1512, 1448, 1278. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 7.37-7.68 (8H, m, H_{arom}), 8.02 (1H, d, $CH_{hydroxy\text{-}naphtoic}$), 8.22 (1H, d, $CH_{3\text{-}hydroxy2\text{-}naphtoic}$), 8.32-8.43 (3H, m, CH_{arom}), 8.73 (1H, s, $CH_{hydroxy\text{-}naphtoic}$), 11.95 (1H, s, OH); Anal. calcd. for $C_{25}H_{15}N_3O$: C, 80.41; H, 4.05; N, 11.25. Found: C, 80.76; H, 4.11; N, 11.68.

3-Phenylphenanthro[9,10-e][1,2,4]triazine (7b): IR (KBr, ν_{max}, cm^{-1}): 3059, 1624, 1599, 1510, 1448, 1278. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 7.69-9.36 proton of aromatic ring. ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 124.31, 124.42, 126.56, 127.41, 127.80, 128.50, 129.03, 129.38,129.65, 131.14, 131.60, 132.17, 133.37, 133.86, 135.65 ($C_{arom.}$), 142.86, 144.92, 160.10 (C=N). Anal. calcd. for $C_{21}H_{13}N_3$: C, 82.06; H, 4.26; N, 13.67. Found: C, 79.87; H, 4.32; N, 13.60.

3-Methylphenanthro[9,10-e][1,2,4]triazine (7c): IR (KBr, ν_{max}, cm^{-1}): 3088, 2928, 2856, 1606, 1510, 1450, 1425, 1373. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 3.07 (3H, s, CH_3), 7.8.85-8.86 (8H, m, CH_{arom}). Anal. calcd. for $C_{16}H_{11}N_3$: C, 75.38; H, 4.52; N, 17.13. Found: C, 75.15; H, 4.38; N, 17.18.

9-(Pyridin-3-yl)acenaphtho[1,2-e][1,2,4]triazine (8a): IR (KBr, ν_{max}, cm^{-1}): 3134, 1614, 1560, 1419, 1321. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 7.67-7.71 (1H, dd, $H_{pyridine}$), 7.95-8.59 (6H, m, H_{arom}), 8.85-8.87 (2H, m, $H_{pyridine}$), 9.13 (1H, s, $H_{pyridine}$). ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 124.27, 124.62, 126.18, 128.75, 129.24, 129.83, 130.04, 131.34, 131.76, 133.49, 134, 135.85 ($C_{arom.}$), 149.08, 152.13, 155.58, 157.38, 159.42 (C=N); Anal. calcd. for $C_{18}H_{10}N_4$: C, 76.58; H, 3.57; N, 18.85. Found: C, 77.07; H, 3.43; N, 18.38.

9-(Furan-2-yl)acenaphtho[1,2-e][1,2,4]triazine (8b): IR (KBr, ν_{max}, cm^{-1}): 3036, 1684, 11614, 1575, 1433, 1329. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 6.81 (1H, t, ^3J = 1.70 Hz, H_{furan}), 7.55 (1H, d, CH_{arom}), 7.90-7.98 (1H, dd, H_{arom}), 8.07 (1H, bs, H_{furan}), 8.29-8.50 (4H, m H_{arom}). ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 113.31, 115.05, 123.77, 125.91, 128.93, 129.22, 129.69, 129.71, 129.94, 130.89, 133.25, 133.75 ($C_{arom.}$), 147.14, 150.63, 154.33, 154.86, 157.07 (C=N, C-O); Anal. calcd. for $C_{17}H_9N_3O$: C, 75.27; H, 3.34; N, 15.49. Found: C, 75.70; H, 3.40; N, 15.68.

2-(Acenaphtho[1,2-e][1,2,4]triazin-9-yl)naphthalen-1-ol (8c): IR (KBr, ν_{max}, cm^{-1}): 3474, 3036, 1637, 1575, 1535, 1421, 1315. ^1H NMR (DMSO-d_6, 300 MHz) δ_H: 7.36-8.69 (11H, m, CH_{arom}), 9.2 (1H, s, $H_{hydroxy\text{-}naphtoic}$), 12.94 (1H, s, OH); Anal. calcd. for $C_{23}H_{13}N_3O$: C, 79.53; H, 3.77; N, 12.10. Found: C, 78.98; H, 3.67; N, 12.68.

RESULTS AND DISCUSSION

A diverse set of 1,2,4-triazines by using benzil were synthesized with optimized conditions. Encouraged by these results, we replaced the phenanthrene-9,10-dione (**2**) or acenaphthylene-1,2-dione (**3**), instead of benzil in same conditions (Fig. 1, Table-1).

The catalyst was tested in the three-component condensation of benzil, nicotinic acid hydrazide and ammonium acetate as a model reaction. After some experimentations with

TABLE-1
PREPARATION OF 1,2,4-TRIAZINES CATALYZED BY $NaHSO_4/SiO_2$

Product	R	Time (h)	Yield (%)[a,b]	m.p. (ºC)
6a	Pyridin-4-yl	4.0	80	158-160
6b	Furan-2-yl	4.0	78	176-178
6c	Pyridin-3-yl	4.0	82	171-173
6d	2-Hydroxynaphthalen-3-yl	4.0	75	206-208
6e	4-Hydroxyphenyl	4.0	79	224-226
6f	Phenyl	4.0	80	148-150
7a	2-Hydroxynaphthalen-3-yl	4.5	72	290-293
7b	Phenyl	4.5	75	178-180
7c	Methyl	4.5	58	160-163
8a	Pyridin-3-yl	4.5	73	217-219
8b	Furan-2-yl	4.5	70	224-226
8c	2-Hydroxynaphthalen-3-yl	4.5	69	162-165

[a]Reaction conditions: temperature (125 ºC), $NaHSO_4/SiO_2$ (0.1 g)
[b]Yields refer to isolated products.

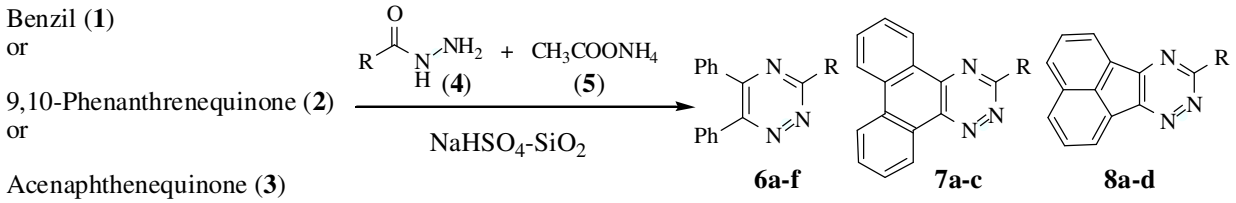

Fig. 1. Synthesis of trisubstituted 1,2,4-triazines using $NaHSO_4/SiO_2$

respect to the catalytic systems and reaction temperatures, the optimal conditions have been established (Table-2). It was found that the SiO_2 as a solid support gave low yield of the product (Table-2, entry 1). This reaction was also performed in the bulk $NaHSO_4$ when the $NaHSO_4$ is not supported. However, the yield of **6c** was low (Table-2, entry 2).

Table-2 shows that the $NaHSO_4/SiO_2$ supported catalyst is active for the production of **6c**. The effect of temperature was studied by carring out the model reaction at different temperatures in $NaHSO_4/SiO_2$ supported catalyst. It was observed (Table-2, entries 3-5) that yield increased as the reaction temperature was raised.

TABLE-2
OPTIMIZATION OF REACTION FOR SYNTHESIS OF **6c**

Entry	Catalyst	Temp. (ºC)	Time (h)	Yield (%)[a]
1	SiO_2	125	4	15
2	$NaHSO_4$	125	4	45
3	$NaHSO_4/SiO_2$	125	4	82
4	$NaHSO_4/SiO_2$	110	4	59
5	$NaHSO_4/SiO_2$	90	4	38

[a]Yields refer to isolated products.

In these experiments, the reaction mixture isolated with acetone and the remaining catalysts dried at 50 ºC for 1 h and then reloaded with fresh reagents for further runs. Apparently, recycling of catalyst is possible for three successive times without significant loss of activity (Table-1, **6c**).

Conclusion

In summary, this paper describes a convenient and efficient process for the synthesis of 1,2,4-triazines through the three-components coupling of benzil or phenanthrene-9,10-dione or acenaphthylene-1,2-dione, with acid hydrazides and ammonium acetate using $NaHSO_4/SiO_2$ as a solid support. This method not only affords the products in excellent yields under solvent free conditions but it is non-volatile, recyclable, non-explosive, easy to handle and thermally robust.

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